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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,698	09/08/2000	Samuel C Silverstein	60467/JPW/GJG	3655

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EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/658,698	SILVERSTEIN ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *17-32* is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 33-132 have been canceled previously.

Claims 1-32 are currently pending.

In view of Applicant's arguments filed November 17, 2004 only the following ground of rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-16 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It was previously stated: "Briefly, the claims are most broadly drawn to a method of inducing an immune response in a subject having a disease to an antigen. The method includes a) loading the antigen and adenosine triphosphate into a particle, b) coating the particle with a ligand of antigen presenting cells, c) incubating the coated particles with antigen presenting cells (APCs), and d) administering the APCs to the subject and generating an immune response to the antigen.

In the "First Series of Experiments" at pages 32-34 and Table 1 on page 35 of the specification it is disclosed that dendritic cells primed in this manner were capable of stimulating the proliferation of T cells in a standard *in vitro* thymidine-uptake assay, asserting that the assay represent a "CTL assay" at page 35, lines 1-7. However, CTL activity as a measure of specific cellular immunity is more accurately reflected by a cytotoxicity assay, such as a ^{51}Cr-release assay or a cytokine profile. It is well established in the art that cellular immunity, mediated by NK cells and killer T cells, is a Type 1 activity and that humoral immunity, mediated by antibodies, is a Type 2 activity (see, *e.g.*, page 188, column 1 of Grufman et al (U on PTO-892)).

It is respectfully submitted that it would require an undue amount of experimentation on the part of one skilled in the art to practice the claimed invention. Grufman et al in the paragraph bridging the columns on page 1088 discloses that IL-12 is required for Type 1 responses to cancer antigens and some bacterial antigens, while not being crucial for some other bacterial infections or viral infections. The la Sala et al 2001 reference (V on PTO-892) discloses that incubating dendritic cells in ATP during maturation, *i.e.*, antigen loading, distorts said maturation and inhibits the production of IL-12 by the matured dendritic cells and impairs their ability to initiate Type 1 immune responses *in vitro* (abstract and column 1 of page 1614 in particular). Accordingly, based upon the state of the art, the artisan would not be able to predict that the dendritic cells generated by the claimed method would be able to stimulate an effective killer T cell response to any antigen in vivo, irrespective of whether the T cells are stimulated by the dendritic cells *in vivo* (claims 1-16) or *in vitro* (claims 17-32).

Additionally, and in particular regard to the method of claims 1-16, the specification does not demonstrate, or reasonably suggest success of, the ability of those same dendritic cells to attract cytotoxic T cells *in vivo*. The la Sala *et al* 2002 reference (W on PTO-892) discloses that dendritic cells that are treated with extracellular ATP possess a reduced capacity for attracting Th1 and T-cytotoxic (killer) 1 cells. One skilled in the art would not be able to predict that dendritic cells which were primed in vitro in the presence of extracellular ATP would be able to attract Type 1 killer T cells *in vivo* for activation versus the loaded antigen.

In view of the lack of predictability in the art to which the invention pertains and the lack of established clinical protocols for therapies based upon the *in vivo* or *in vitro* activation of T cells using artificially manipulated APCs, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inducing a cytotoxic response to an antigen *in vivo*."

In response to Applicant's arguments filed April 19, 2004, it was stated:

"Applicant argues that the references cited cannot be used to cast doubt on Applicant's claimed invention because Grufman teaches only the incubation of APCs with peptide, but without ATP and la Sala teaches only the extracellular application of ATP, while the vesicles of the instantly claimed invention direct the ATP via phagolysosomes directly into the cytoplasm. This is not convincing because ATP is an intracellular messenger, not an extracellular messenger. In order for the ATP to exert an effect upon cells as in the la Sala reference, it must be taken up by the cells and is therefore present in the cytoplasm - similar to the instant invention. Accordingly, absent a showing that there is a functional difference between the instantly claimed invention and the teachings of la Sala and Grufman, the specification is not seen as being enabled for the in vitro stimulation of APCs for the generation of an immune response in vivo."

Applicant's arguments filed November 17, 2004 have been fully considered but they are not persuasive.

Applicant argues that the Grufman reference of record is not applicable because Grufman does not teach Applicant's claimed invention. This statement lacks merit because Grufman was not cited as a prior art reference anticipating or obviating the claimed invention. Rather, Grufman was relied upon for the disclosure regarding the need for IL-12 in Type I reactions. This disclosure was viewed in light of the la Sala reference of record, which disclosed that application of ATP to dendritic cells during maturation inhibits IL-12 production.

Applicant argues further that la Sala is not applicable because la Sala applies the ATP extracellularly while the instantly claimed invention, though the use of a delivery vehicle, applies the ATP intracellularly. Applicant concludes, therefore, "the different methods of introduction of the ATP in La Sala and the instant invention are evidence of a functional difference between the references and the claimed methods." Again, Applicant appears to be applying the standards required for a reference cited for anticipation or obviousness. Contrary to Applicant's position, both references were applied correctly for disclosure of principles involved in a cytotoxic immune response showing that, in view of the state of

the art at the time the invention was made, the artisan would not be able to predict that the claimed method would be functional for the stimulation of a cytotoxic T cell response. Applicant asserts in the response that the different method of ATP application in the la Sala reference constitutes a functional difference from the instant method and cannot be used to show that the claimed method is not enabled. However, an argument that there is a functional difference is not equivalent to a showing of a functional difference. Applicant has failed to explain why, other than the use of a vehicle, the application is indeed different. ATP is an intracellular messenger, not an extracellular effector of cellular functions. In order for the ATP to exert an effect upon cells as in the la Sala reference, it must be taken up by the cells and is therefore present in the cytoplasm - similar to the instant invention. While the ATP is applied to the dendritic cells in a different manner, the mode of action of ATP upon cellular functions is intracellular in both methods and therefore is the same.

Applicant further argues that a working example of the claimed invention was provided in the specification at pages 32-35. However, as stated previously (reproduced *supra*), the working example in the specification is a thymidine-uptake assay. This assay is well known in the art to be a measure of the proliferation of T cells, showing proliferation by incorporation into the cells of thymidine nucleotides bearing a radioactive marker. This assay reveals an increase in the number of T cells in a sample, but does not provide any information regarding the cytotoxic effector function of the T cells. The effector function of the T cells is shown in the art by well known by assays such as the CTL assay, which measures the release of radioactive label into the external medium by target cells when the target cells are lysed by cytotoxic T cells. Proliferation of T cells and lysis of target cells are not equivalent measurements and an increase in the number of T cells in response to an antigen does not equate to the ability of T cells within that population to lyse a target cell bearing that antigen.

Allowable Subject Matter

2. Claims 17-32 are allowed.

Conclusion

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
February 1, 2005

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
2/1/05